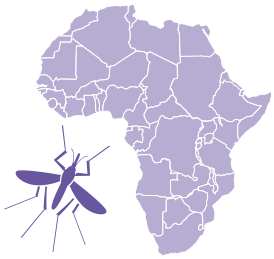
Malaria *and* Pregnancy



Key Research

Increasing drug resistance among certain types of malaria parasites have renewed interest in the problem of malaria in pregnancy and spurred research on the development of new drug treatment options. Since the early 1990s, numerous studies have been conducted (primarily in Africa and Asia) to better understand the complex ways that malaria affects both mother and child and the impact of various drug regimens on preventing or mitigating malarial infection. Summaries of some key research studies follow. (See the enclosed reference list for information on other studies and articles.)

1. Clara Menendez. "Malaria during pregnancy: A priority area of malaria research and control." *Parasitology Today.* Vol. 11, no. 5. 1995.

Clara Menendez emphasizes that although pregnant women are more susceptible to many types of infection than non-pregnant women, this trend is most clear with regard to malaria. In this article, Dr. Menendez discusses the gaps in research on malaria and pregnancy, as follows.

The reasons why pregnant women are so susceptible to malaria. During pregnancy, a woman's physiology adapts to the growth of the fetus, often resulting in suppressed immunity. An increase in hormone and protein production during pregnancy seems to inhibit the immunity of cells. This could explain why young women pregnant for the first time have a greater risk of infection than older women with lower estrogen levels. Immunity also seems to be influenced by exposure to malaria over time and growing resistance by the placenta and blood.

The influence of number of pregnancies on the likelihood of infection. Non-immune women contract malaria at the same rate regardless of how many times they have been pregnant. However, in areas where immunity is high, women who are pregnant for the first time are most vulnerable. Some studies indicate that women who have had more than 5-7 pregnancies are also at high risk.

The influence of nutrition on risk of infection. It seems logical that higher levels of iron and folic acid would make a woman stronger, and thus prevent infection. Previous studies had raised concerns that iron supplementation could increase the risk for malaria infection. However, more recent studies have indicated that normal levels of micronutrient supplementation do not increase rates of malaria among pregnant women (with the exception of those with the sickle cell trait).

The increase in stillbirths and miscarriages during malaria epidemics. This connection is likely due to the presence of parasites in the placenta and the subsequent blockage of nutrients from mother to fetus, or it may be due to high fever or because of low oxygen to the baby because of maternal anemia.

The influence of maternal malaria on infant health and mortality. Infection of the placenta inhibits oxygen flow and, in turn, retards fetal growth and spurs premature birth. In addition, infected women are more likely to give birth to anemic infants. Both anemia and hypoglycemia in mothers are connected to high rates of low birthweight babies, who have much less chance of surviving their first year of life.

Relatively low rates of malaria among newborns. It is possible that a mother's white blood cells help prevent the transmission of malaria to the fetus, or that she gives effective antibodies to the fetus. Another theory is that the immune system of a fetus may be activated by the presence of malaria. Although infants may gain from the transmission of malarial antibodies from their mothers, this benefit is outweighed by the problems caused by malarial infection (such as low birthweight and subsequent infant mortality).

The efficacy of preventive drug treatment. Some courses of treatment appear to be highly effective in reducing the ill effects of maternal malaria. However, it is also possible that drugs can inhibit the development of immunity in the fetus. Furthermore, scarce resources, a lack of compliance by patients, and the emergence of drug-resistant strains of malaria compromise the value of drug treatment. Despite such obstacles, field studies have clearly established that the benefits of treatment are far greater than the risks.

The development and use of a malaria vaccine. Whether or not a vaccine could prevent maternal malaria likely depends on three factors: a woman's level of immunity before pregnancy; the stage of parasite growth; and the point in pregnancy when the vaccination is given.

2. P.A. Phillips-Howard. "Epidemiological and control issues related to malaria in pregnancy." *Annals of Tropical Medicine and Parasitology.* Vol. 93, no. 1. 1999.

In November 1997, a symposium on malaria in pregnancy was held in Kisumu, Kenya, to identify medical and scientific research, disease trends, health impacts, and intervention strategies. In this article, P.A. Phillips-Howard identifies the key issues discussed at the symposium and actions that should be taken by researchers, as follows.

Clinical trends. Despite the fact that rates of malaria infection vary widely among countries and specific areas, the impact of the disease on health appears to be similar everywhere. For example, a reduction in birthweight of about 128 grams has been observed among the babies of women exposed to *Plasmodium falciparum* (the most dangerous malaria parasite) both in sub-Saharan Africa and along the Thai-Burmese border. Almost all of these women did not exhibit clear symptoms of malaria themselves because infection can be undetectable for up to four months. In addition, the negative impact of *Plasmodium vivax* (another key strain of malaria) appears to be greater than previously thought.

Women and HIV. Initial research indicates that pregnant women are more likely to get malaria and to have higher concentrations of malarial parasites if they are infected with the HIV virus. This seems to be the case even for women who have had multiple pregnancies, although normally this group would have considerable immunity to malaria. In addition, one study indicated that infant mortality among the children of HIV-positive mothers was 3-4 times higher when the mother had malaria than when she didn't.

Clinical indicators. The worst effects of malaria are reflected in maternal mortality, which can be difficult to measure and clearly link to a single cause. More specific measurements of malaria rates and impacts include maternal anemia, low birthweight, fetal growth retardation, and parasite levels in the placenta and blood.

Anti-malarial drugs. The provision and effectiveness of drugs has been inhibited by the emergence of drug-resistant strains of malaria. Other problems include a lack of financial resources to purchase drugs, inadequate systems to administer them, and poor compliance with treatment regimens by patients.

To date, treatment of pregnant women twice a month with a combination of pyrimethamine and dapsone has been shown to reduce anemia and low birthweight. Similarly, a regimen of two or more doses of sulfadoxine-pyrimethamine (SP) has been effective in reducing maternal anemia and malarial infection of the placenta and blood. Even partial compliance with this regimen has an effect, while more doses seem to have a positive impact on HIV-positive women. Chloroquine may still be effective in areas where resistance to it is low. Research is currently underway to test the safety and efficacy of artemsinin derivatives, and a drug known as LAPDAP may yet prove useful.

Treatment during pregnancy. A person can have a malarial infection but still not have symptoms. For pregnant women who develop a fever, however, treatment that aims to achieve a total cure becomes imperative. Quinine is one useful drug with which to treat malaria in pregnancy because it is safe; however, it must be administered three times daily. SP is increasingly prescribed, but good surveillance systems need to be put into place to ensure that repeat dosing is not associated with side effects.

Other interventions. Research has shown that pregnant women who take iron have babies with increased birthweights and hemoglobin levels. However, the link between iron supplementation and malaria has not yet been studied, although some evidence exists that folic acid supplementation may compromise the efficacy of SP treatment. Some studies indicate that the use of bed nets treated with insecticides can reduce rates of malaria among pregnant women, while others do not show any effect.

Delivery systems. Efforts to prevent malaria should be integrated into prenatal and other health care services. Although national programs will vary according to trends and resources, the provision of "package care" for pregnant women (including tetanus shots, micronutrient supplementation, and treatment with an anti-malarial drug) seems to be an effective approach.

Next steps for researchers.

- Define and standardize indicators to assess the specific effects of malaria in pregnancy; criteria with which to measure responses to drug treatment; tests to measure the effects of anti-malarial drugs.
- Improve collaboration among researchers at different sites and between scientists and malaria control programs.
- Compare the advantages, disadvantages, risks, and benefits of different anti-malarial treatments.
- Investigate alternatives to SP because of indications that resistance to this relatively new drug is increasing.
- Research how to modify behavior during pregnancy, e.g., improving compliance with drug and micronutrient supplement regimens.
- Target adolescent girls and young women before their first pregnancy to encourage the use of prenatal and other health services.
- Examine how to scale up research interventions, including monitoring and evaluation of what works and what does not.
- Develop field sites to monitor the safety, efficacy, and quality of interventions.
- Investigate the role and dosing regimens of iron and interactions between folic acid and SP during pregnancy and between iron supplementation and the sickle cell trait.
- Evaluate cases of adverse drug reactions and develop accessible databases with relevant information.
- Assess the influence of HIV status on drug safety and efficacy. Explore the public health implications of a link between HIV and malaria.

- Investigate initial findings that single malaria infections have similar effects on birthweight and anemia as do multiple infections.
- Examine the efficacy of insecticide-treated bed nets in controlling malaria in various settings; compare with the effectiveness of anti-malarial drug treatment.
- Design a protocol to manage and treat disease in pregnant women.

3. Linda J. Schultz, Richard W. Steketee et al. "The efficacy of antimalarial regimens containing sulfadoxine-pyrimethamine and/or chloroquine in preventing peripheral and placental *plasmodium falciparum* infection among pregnant women in Malawi." *American Journal of Tropical Medicine & Hygiene.* Vol. 51, no. 5. 1994.

According to World Health Organization guidelines, all pregnant women living in areas where malaria is widespread should receive regular preventive treatment. Studies in east Africa in the early 1990s indicated that chloroquine (CQ)—the longstanding "drug of choice"—was no longer effective in many areas because drug-resistant strains of malaria were emerging. In contrast, new drugs (such as mefloquine) appeared to reduce infection of the placenta by malaria parasites and, in turn, the prevalence of low birthweight babies.

In response to these findings, the National Malaria Control Committee of Malawi decided to test the relative efficacy of some affordable anti-malarial drug regimens. The article by Linda Schultz, Richard Steketee et al. describes a study conducted in Mangochi District in southern Malawi in March-October 1992. The research aimed to compare the impact of sulfadoxine-pyrimethamine (SP) on rates of placental infection among pregnant women with that of CQ.

Scope of the study. A total of 357 women were selected as study subjects. All were between 16-32 weeks of gestation and in their first or second pregnancies, attended rural prenatal clinics, and consented to take anti-malarial drugs and participate in the study. Following a routine prenatal examination, the women answered a questionnaire on such aspects as their age, education, socioeconomic status, and illness or treatment during their current pregnancy. No significant variations in these aspects were found among the subjects.

The women were also weighed and measured and blood was drawn to test for the presence of malarial infection and red blood cell levels (which indicate anemia). Throughout the study, a woman was considered infected if malaria parasites were detected; the same standard was applied to determine infection of the placenta following delivery. Infants weighing less than 2.5 kilograms 24 hours after birth were defined as having low birthweight.

Treatment. The study subjects were divided into three groups for treatment with different anti-malarial drugs. The first group (104 women) received an initial dose of CQ, followed by weekly doses of CQ until delivery. The second group (117 women) was given an initial dose of SP, followed by weekly doses of CQ until delivery. The third group (136 women) received an initial dose of SP, followed by a second dose at the beginning of the third trimester.

All the women attended follow-up visits at which they were questioned about whether they had experienced fever or side effects from the anti-malarial drugs or had used other medications. Their blood was drawn monthly and tested for malaria infection.

Delivery and after. Fifty women were lost from the study during follow-up. The 179 (58 percent) of the study subjects who delivered in a hospital were weighed, answered a basic questionnaire, and had blood drawn for hemoglobin and malaria tests. Following delivery, blood from the mother's side of the placenta was collected and tested for the presence of malarial parasites.

The general health status of all newborns (including those delivered at home) was examined when they were 3-7 days old and one month old. In addition, interviews were conducted with the mothers of infants who died to ascertain possible cause of death.

Efficacy of the drug regimens. At the time of enrollment in the study, approximately 67 percent of the women in each group tested positive for malaria parasites. Changes in their conditions are summarized in the table below.

Study group	Infection rate, 3 weeks after initial treatment	Infection rate at delivery	Placental infection at delivery, malaria (wet) season	Rate of premature babies	Rate of low birthweight babies
1. (CQ)	24%	32%	47%	31%	27%
2. (SP/CQ)	0-4%	14%	37%	19%	15%
3. (SP)	0-4%	3%	10%	21%	17%

Conclusions. **The most effective treatment regimen for clearing malaria parasite infections was followed by the third group, i.e., both initial and follow-up doses of SP.** It was found that intermittent SP treatment allows for lengthy periods of time when the placenta is uninfected, which in turn fosters the normal transference of nutrients from mother to fetus and normal fetal growth. In addition, women in groups two and three had better weight gain during pregnancy than those in group one.

Another advantage of the SP regimen is that it requires only two doses administered at prenatal clinics. This ensures a higher level of compliance than the CQ regimen, which requires women to administer the doses themselves every week at home. Importantly, women taking SP reported fewer side effects than those taking CQ. Further research is required to definitely establish the safety of SP during pregnancy and to better understand its side effects. However, it is already clear that this relatively new drug regimen is both medically advantageous and cost-effective in preventing and treating malaria in pregnancy.

4. F.O. Ter Kuile, D.J. Terlouw et al. "Permethrin-treated bed nets reduce malaria in an area of intense perennial malaria transmission in western Kenya" (forthcoming).

This study focused on the use of insecticide-treated bed nets in preventing malaria. It was part of a larger, community-based research endeavor on the impact of bed nets in reducing childhood mortality in 75 villages in western Kenya. Half of the villages received bed nets in January 1997 and half two years later.

A total of 723 women in 15 villages were visited monthly throughout their pregnancies. Each time, a questionnaire on health and symptoms was administered and a blood sample taken to test for red blood cell levels and infection with malaria parasites. Such data was collected from 1,522 women in the other 60 villages only at the time of their deliveries. All the women received routine prenatal care.

A preliminary analysis of results indicates that women in their first, second, or third pregnancies living in villages that used bed nets were much less likely to develop infections with malaria parasites than those in other villages. They were also less likely to become anemic during pregnancy. Bed nets thereby seem to contribute to reduced rates of low birthweight and premature babies.